Effects of multiple inherited and acquired thrombophilia on outcomes of in-vitro fertilization

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Effects of multiple inherited and acquired thrombophilia on outcomes of in-vitro fertilization

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Abstract

Introduction: The effects of multiple inherited and acquired thrombophilic defects on the outcome of in-vitro fertilization (IVF) remain unexplored. The aim of this study was to evaluate the association between multiple thrombophilia and clinical outcomes in a large prospective cohort of women undergoing IVF.

Materials and Methods: Consecutive women scheduled for IVF were eligible. The primary study outcome was live birth. Secondary outcomes included spontaneous abortion, clinical pregnancy, and symptomatic venous thromboembolism.

Results: 687 women with a mean age of 34.6 (±3.2) years were included. Overall, 22 women (3.2%) had two or more thrombophilic defects. The probability of live birth was not statistically significantly different between women with ≥2 thrombophilia (odds ratio [OR] 0.62; 95% confidence interval [CI], 0.18 to 2.11) or ≥1 thrombophilia (OR 0.67;95% CI, 0.41 to 1.09) and women without any thrombophilia. None of the individual inherited thrombophilia nor positivity to antiphospholipid antibodies or lupus anticoagulant were associated with live birth. Single positivity for lupus anticoagulant carried a more than threefold higher risk of abortion (OR 3.74; 95% CI, 1.30 to 10.75). There were no statistically significant associations between individual or multiple thrombophilic defects and clinical pregnancy or pregnancy test results. No woman had a history of venous thromboembolism and none developed a thrombotic event during the study.

Conclusions: In women undergoing IVF, the presence of two or more thrombophilic defects was rare and showed no statistically significant associations with IVF outcomes.

Keywords: assisted reproductive technique; thrombophilia; live birth; spontaneous abortion; prospective studies.

Highlights

- The presence of two or more thrombophilic defects was infrequent in women undergoing in-vitro fertilization
- The effects of multiple thrombophilic defects on outcomes of in-vitro fertilization remain unclear.
- Live birth was lower with one or more thrombophilia, albeit differences were not significant.

Abbreviations

CI = Confidence Intervals

IVF = In-Vitro Fertilization

OR = Odds Ratio

Introduction

The failure rate of assisted reproductive techniques such as in-vitro fertilization (IVF) remains as high as 60-70% causing intense emotional distress in women undergoing these procedures [1-2]. The pathophysiology behind the high failure rate is largely unexplained and likely multifactorial [3]. One of the potential mechanisms includes the abnormal coagulation activation at the maternal–fetal interface leading to thrombosis of the placental vessels and secondary implantation or placentation failures [4]. In a previous systematic review on the association between thrombophilia and outcomes of assisted reproduction techniques, we summarized the evidence from 33 studies involving 6,093 patients and found that women with IVF failures tested more frequently positive for factor V Leiden and antiphospholipid antibodies [5]. However, these associations were only observed in case-control studies with a number of methodological limitations and were not confirmed in prospective cohorts. Since that meta-analysis, few other studies evaluated the potential influence of thrombophilia on the outcomes of IVF. In a large prospective cohort of 1,717 women undergoing fresh non-donor IVF cycles, none of the eight inherited thrombophilia seemed to predict clinical pregnancy, live birth, or pregnancy loss [6]. In a retrospective analysis of 594 women with unexplained infertility initiating IVF treatment, none of the thrombophilia tested were significantly associated with the number of IVF cycles nor with lower fertility success rate [7]. Unexpectedly, carriers of factor V Leiden and lupus anticoagulant had significantly higher live birth rates (12.3% and 12.6%, respectively) in comparison to women who tested negative (9.0% and 9.7%, respectively). These and previous observations focused on inherited thrombophilia or separately evaluated individual thrombophilic defects without assessing the potential effects of multiple inherited and acquired thrombophilia that remain therefore unexplored.

The aim of this study was to evaluate the association between multiple inherited and acquired thrombophilia and clinical outcomes in a large prospective cohort of women undergoing IVF.

Materials and Methods

Study population

Consecutive women scheduled for IVF were eligible for this study. Exclusion criteria were an ongoing or indication for anticoagulant treatment, thrombophilia screening not available before IVF, age ≥ 40 years, embryo transfer not performed, lack of informed consent. The study was approved by the local institutional review board and all women signed a written informed consent before study procedures. The study is registered in clinicaltrial.gov with accession number NCT02407730.

Study outcomes

The primary study outcome was live birth. Secondary outcomes were spontaneous abortion, clinical pregnancy and symptomatic venous thromboembolic events occurring during the IVF procedure and, in case of pregnancy, during the gestation period up to 6 weeks post-partum. For descriptive purposes, we recorded positive pregnancy tests and pregnancy-related complications which included preeclampsia, placental abruption, and intrauterine growth retardation. Pregnancy test was performed by measuring β-human chorionic gonadotropin 14 days after the embryo transfer. A viable (clinical) pregnancy was defined as a pregnancy diagnosed initially by serum β-human chorionic gonadotropin levels with evidence of one or more gestational sacs at six weeks gestation. The clinical pregnancy rate was defined as the proportion of women achieving a clinical pregnancy out of the total number of women undergoing embryo transfer. The live birth rate was the number of deliveries divided by the total of women undergoing the procedure. The risk of abortion was defined as the risk of pregnancy loss out of all women who underwent the procedure. The study considered only the outcomes of fresh non-donor embryo transfers.

Study procedures

All patients underwent controlled ovarian stimulation, follicle growth monitoring, and ovum pick-up as previously described [8]. All IVF procedures were performed by intracytoplasmic sperm injections. The

embryo transfer took place under ultrasound guidance about 72-76 hours after ovum pick-up. Up to three embryos were transferred in uterus and the number of embryos transferred reflected national guidelines, with some variation according to individual patient needs. The luteal phase was supported with daily intramuscular injections of 100 mg of progesterone (Prontogest, IBSA, Italy).

All women attending our University Center of Reproductive Medicine to undergo IVF have regular clinical visits to closely monitor controlled ovarian stimulation, need for gonadotropin dosage adjustments, and to identify any ensuing complications. As part of the clinical risk assessment, all women undergo thrombophilia testing before IVF, and consult an expert in thrombosis and haemostasis to decide on the potential indications for low-molecular-weight heparin according to the guidelines of the American College of Chest Physicians, which suggest antepartum thromboprophylaxis for women with a history of unprovoked, pregnancy- or estrogen-associated venous thromboembolic events or women with a family history of venous thromboembolism who are homozygous or compound heterozygote factor V Leiden and prothrombin gene mutation [9]. The panel of thrombophilia routinely tested included factor V Leiden, factor II mutation (G20210A), deficiency of protein C, protein S or antithrombin, hyperhomocysteneimia, lupus anticoagulant, anti-cardiolipin and anti-beta2 glycoprotein antibodies. To avoid any potential effect of hormonal stimulation on antiphospolipid antibody levels, blood for thrombophilia measurement was withdrawn and analyzed before IVF procedures [10-11]. All patients with positive lupus anticoagulant or antiphospolipid antibodies repeated testing after 12 weeks. Blood samples were collected in 3.8% trisodium citrate and centrifuged at 4000 g for 15 min to obtain platelet-poor plasma. We measured lupus anticoagulant, anticardiolipin and anti-beta2 glycoprotein antibodies (QUANTA Lite™, INOVA Diagnostics, San Diego, CA), antithrombin and protein C (Berichrom® Antithrombin and Berichrom® Protein C, SIEMENS, Germany), and free protein S antigen (INNOVANCE FREE PS Ag assay, SIEMENS, CT). DNA was extracted from peripheral blood leukocytes according to standard protocols. Factor V Leiden and prothrombin mutation genotyping were performed by a TaqMan® (Applied Biosystems, Foster City, CA) probe-based real time PCR technique.

Data collection

We collected information on demographics (maternal age, body mass index), comorbidities (e.g. prior venous thromboembolism or a family history of venous thromboembolism, cardiovascular disease), personal obstetric history, causes of infertility, prior IVF attempts, concomitant treatments, thrombophilia, results of pregnancy test. Venous thromboembolic events had to be objectively confirmed by standard diagnostic methods which included compression ultrasonography for deep vein thrombosis and computed tomography pulmonary angiography or lung scan for pulmonary embolism [12].

Statistical considerations

Data are reported as frequencies, mean (± standard deviations), and/or median (range). Categorical variables were analyzed with the chi-square test, and continuous variables with a Student t test or Mann–Whitney U test as appropriate. We assessed the association between study outcomes and multiple or individual inherited and acquired thrombophilia. Positivity for lupus anticoagulant or antiphospholipid antibodies that was not confirmed at repeat testing were considered in the analysis as thrombophilic defects because of their potential effects on IVF outcomes [5]. The effect of thrombophilia on primary and secondary outcomes was first evaluated in univariable analysis calculating odds ratio (OR) and the relative 95% confidence intervals (CIs). Other variables that were considered for their potential effect on study outcomes were age, body mass index (kg/m^2), smoking, cardiovascular disease, IVF indication, number of previous cycles, number of previous abortions, previous pregnancies either spontaneous or following intracytoplasmic sperm injections. All explaining variables significantly associated with the outcome at the 0.05 level in univariable models were included in multivariable logistic regression analyses. Explorative subgroup analysis was conducted for the primary study outcome in women with idiopathic infertility and women < 35 years. P-values of 0.05 (two tailed) were considered significant. The sample size was calculated based on a reported success rate of live birth using fresh embryo transfers of 35.5% [13]. We assumed that the prevalence of multiple inherited and acquired thrombophilia defined as two or more thrombophilic defects was about 10%. Assuming 40% live birth in women without any thrombophilia and a relative risk of at least 0.55, 715 women would need to be

included to reach 80% power at two-sided alpha level of 5%. Descriptive and analytical analyses were conducted using IBM SPSS version 19 (SSPS Inc., Chicago, IL, USA). Sample size calculations were done in STATA (StataCorp. 2013. Stata Statistical Software: Release 13. Texas, USA).

Results

From March 2015 to July 2017, a total of 1,008 eligible women were evaluated, of whom 321 were excluded because of an ongoing anticoagulant treatment with low-molecular-weight heparin for ovarian hyperstimulation syndrome (n = 22), IVF cancelled or treatment discontinued for any reason (n = 75), no thrombophilia available before IVF or patients refused measuring any thrombophilia (n = 93), age ≥ 40 years (n = 125), or more than one of above reasons (n = 1, Figure). Five additional patients moved to another IVF center after initial evaluation and were not accessible to follow-up. The final study population consisted of 687 women with a mean age of 34.6 (± 3.2) years. The most frequent indications for IVF were infertility due to tubaric (n = 153, 22%) or male (n = 197, 28.7%) factors, and idiopathic infertility (145, 21.1%). Four women had at least one first-degree family member with a history of venous thromboembolism while none had experienced past venous thrombotic events. Baseline demographic characteristics of study population are reported in Table 1.

Thrombophilia

The number of thrombophilic defects ranged from 0 to 4. A total of 537 (78.2%) women had no inherited or acquired thrombophilia, while the remaining patients had either one (n = 128, 18.6%), two (n = 17, 2.5%), three or more (5, 0.7%) thrombophilic defects. Overall, there were 149 women (22%) with at least one thrombophilia and 22 women (3.2%) with two or more thrombophilic defects. Excluding women with positivity for lupus anticoagulant or antiphospholipid antibodies that was not confirmed at repeat testing, only 16 women (2.3%) had two or more thrombophilia. The most prevalent inherited thrombophilia was factor V Leiden, which was detected in 34 of 624 women tested (5.5%). Deficiencies of protein S, protein C and antithrombin were less common (Table 2). The mean protein S, protein C and antithrombin levels were

89.4% (15.1), 96.5% (14.5), and 101.1% (21.1), respectively. The proportion of women with missing data on individual inherited thrombophilia ranged from 8.4% for protein S to 27% for antithrombin.

Lupus anticoagulant was detected in 20 of 597 (3.3%) patients of whom only two tested again positive at the second measurement performed 12 weeks later. Anticardiolipin antibodies were positive in 31 of 622 (5.0%) patients of whom four tested positive for both IgM and IgG antibodies, 12 for IgG and 15 for IgM antibodies alone. Only two patients (0.3%) had anticardiolipin levels that fulfilled antiphospholipid syndrome criteria (>40 GPL or MPL) and both were of IgM subtype [14]. The median titers of anticardiolipin IgG and IgM antibodies were 1.0 GPL/mL (0 - 32.0) and 1.0 MPL/mL (0 - 70), respectively. Anti-beta2 glycoprotein antibodies were positive in 12 of 467 (4.7%) patients of whom four were positive for both IgM and IgG, four for either IgM or IgG alone. Only three patients - all with IgM subtype - had levels >40 GPL or MPL (0.6%). The median titer of anti-beta2 glycoprotein antibodies was 1.0 U/mL (0 - 28.5) for IgG and 1.0 U/mL (0 - 96.2) for IgM. Only one patient with both anticardiolipin and anti-beta2 glycoprotein antibodies was again positive at the control 12-weeks later. Overall, fifty-seven women tested positive to either anticardiolipin antibodies, anti-beta2 glycoprotein antibodies or lupus anticoagulant and three of them had positivity confirmed at 12 weeks. The proportion of women with missing data ranged from 9.5% for anticardiolipin antibodies to 32% for anti-beta2 glycoprotein antibodies.

Of the four women with a family history of venous thromboembolism, three tested positive for one thrombophilic defect while the fourth had no thrombophilia.

IVF outcomes

Overall, 231 women (33.6%) had a positive pregnancy test and 208 (90%) obtained a clinical pregnancy for a calculated clinical pregnancy rate of 30% (Supplementary Table 1). Eventually, 138 women (20.1%) delivered 178 live children leading to a live birth rate of 26% (178/684). Sixty-four women (9.3%) had spontaneous abortion, two required a therapeutic abortion after the 12th week because of a severe genetic anomaly (trisomy 13 and 18), and a third patient voluntary interrupted gestation. Twenty-two patients had at least one pregnancy complication, which included preeclampsia (n = 5), placental abruption (n = 2), and

intrauterine growth retardation (n = 8). Seven women had an ectopic pregnancy. Three patients moved to another center after the IVF procedures and follow-up was not available.

None of the participating women received antepartum thromboprophylaxis, whereas post-partum low-molecular-weight heparin prophylaxis was administered to 89 patients (13%) who underwent caesarean section. There were no venous thromboembolic events during IVF procedures, gestation or the peripartum period. One patient developed superficial vein thrombosis of the forearm following parenteral iron infusion during gestation.

Thrombophilia and IVF outcomes

The odds of a live birth was not significantly different between women with ≥2 thrombophilia and women with no thrombophilic defects (OR 0.62; 95% CI, 0.18 to 2.11; Table 3). Similarly, there were no statistically significant associations of multiple thrombophilia with abortion (OR 1.56; 95% CI 0.45 to 5.41), clinical pregnancy (OR 0.86; 95% CI, 0.33 to 2.23), or positive pregnancy tests (OR 0.73; 95%CI, 0.28 to 1.90) (Supplementary Tables 2 to 4).

Compared to women with no thrombophilic defects, the odds of a live birth was not statistically significantly different in women with one or more thrombophilia (OR 0.67; 95% CI, 0.41 to 1.09). The presence of one or more thrombophilic defect seemed associated with a higher risk of abortion, whereas no association was observed with clinical pregnancy or positive pregnancy test (Supplementary Table 2 to 4).

The direction of the association estimates of individual thrombophilic defects were typically towards lower rates of live birth and higher risk of abortion compared to no thrombophilia, but these associations were not statistically significant (Table 3 and Supplementary Table 2). Women with lupus anticoagulant had a more than threefold higher risk of abortion compared to women without lupus anticoagulant (9.6% versus 2.8%, OR 3.74;95% CI, 1.30 to 10.75). There were no statistically significant associations between individual thrombophilia and clinical pregnancy or pregnancy test results, and direction of these associations varied (Supplementary Tables 3 and 4).

Age, body mass index, smoking, cardiovascular disease, indication for IVF, number of previous IVF cycles, history of abortion, or previous spontaneous or assisted pregnancies had no significant effect on live birth nor abortion. The odds of a positive pregnancy test was lower in older women with a 6% reduction for each additional year of age (OR 0.94; 95% CI, 0.90 to 0.99). Previous pregnancy after intracytoplasmic sperm injections carried higher chances of a positive pregnancy test result (OR 1.89; 95% CI, 1.10 to 3.23) and clinical pregnancy (OR 1.76; 95% CI, 1.02 to 3.03).

Discussion

In women undergoing IVF, the presence of two or more thrombophilic defects is rare. Our study did not detect statistically significant associations between multiple thrombophilia and live birth, abortion, clinical pregnancy, or positive pregnancy test.

A previous meta-analysis found an inconsistent association between thrombophilia and IVF outcomes [5]. While case-control studies suggested that infertile women tested more frequently positive for anti-phospholipid antibodies than fertile controls, cohort studies did not confirm a significant association between anti-phospholipid antibodies and live birth. Recent studies have also reported conflicting results. In a large prospective cohort of 1,717 women undergoing IVF, Patounakis and colleagues found that none of the eight inherited thrombophilia predicted IVF outcomes [6]. Antiphospholipid antibodies and lupus anticoagulant were not evaluated and about 16% of women received antithrombotic treatment. In a retrospective analysis of 594 women with unexplained infertility initiating IVF, positivity for factor V Leiden and lupus anticoagulant were unexpectedly associated with higher live birth rates [7]. Interestingly, three other studies showed a potential benefit of factor V Leiden mutation [15-17]. Along the same line, recent data suggested that the association between thrombophilia and recurrent pregnancy loss or pregnancy complications is weak and does not translate into large absolute increased risk of recurrent complications [18-23].

With the exception of lupus anticoagulant, which seemed to increase the odds of spontaneous abortion by more than threefold, none of the individual thrombophilia was statistically significantly

associated with IVF outcomes, although the direction of the associations typically suggested lower live birth and higher risk of abortion. The relatively low prevalence and the difficulty in obtaining adequate measurements of lupus anticoagulant in every laboratory remain major obstacles. There were no venous thromboembolic events during IVF or gestation, consistent with data from previous studies, which indicated no or very modest thrombotic risk with IVF [24-28].

Strengths of the current study include the prospective evaluation of multiple thrombophilia in a relatively large population undergoing standard IVF procedures. There are, however, some limitations that need to be acknowledged. Since not every woman got tested for all thrombophilia, reflecting a real-world scenario, we may have underestimated the risk associated with some thrombophilia. Partial testing of thrombophilia in the same individual was often related to the patient's decision to proceed to IVF avoiding further delays caused by laboratory testing. Our study lacked statistical power, because the prevalence of women with two or more thrombophilia and observed effects were smaller than anticipated. Although some of the observed associations may be due to chance, the odds of lower live birth and higher abortion rates are tenable. To avoid the confounding effect of age, we included women younger than 40 years and the current findings may not apply to older women in whom the role of thrombophilia, if any, remains to be elucidated. Early reports on the association between thrombophilia and outcomes of assisted reproductive techniques fostered the adoption of antepartum aspirin or low-molecular-weight heparin to increase pregnancy rates, despite limited and conflicting evidence to support their use [29-34]. Currently available evidence on the association between thrombophilia and IVF outcomes is very weak and questions the use of antithrombotic agents in women undergoing IVF.

Conclusion

The presence of two or more thrombophilic defects is uncommon in women undergoing IVF. Because of the imprecision in the estimates, the current study provides very weak evidence for an association between multiple thrombophilia and lower odds of live birth and higher risk of abortion. While larger studies may inform the debate about the effects of thrombophilia on IVF outcomes, the rarity of multiple thrombophilic defects questions their clinical relevance. Furthermore, the rare occurrence of multiple thrombophilia poses a major obstacle to perform an adequately powered study.

Authors' roles

Concept and design: MDN, GMT, EP. Interpretation of data, critical writing or revising the intellectual content, and final approval of the version to be published: MDN, AP, GMT, MDG, AWSR, EP.

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None.

Conflict of interest

None of the authors have potential conflicts of interest to declare in relation to the current work.

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Table 1. Baseline characteristics of study population

Characteristic	N = 687
Age, years, mean (SD)	34.6 (3.2)

Body mass index, kg/m^2, mean (SD)	22.9 (4.1)
Smoking	
Current	99 (14.4)
Previous	11 (1.6)
Previous venous thromboembolism	0
Family history positive for venous thromboembolism	4 (0.6)
Aspirin	6 (0.9)
Indication for IVF	
Ovulatory	59 (8.6)
Tubaric	153 (22.3)
Endometriosis	55 (8.0)
Male	197 (28.7)
Unexplained	145 (21.1)
Uterus	12 (1.7)
Recurrent abortion	5 (0.7)
Multiple	61 (8.9)
Previous IVF cycles	
0	417 (60.9)
1	153 (22.3)
≥2	115 (16.8)
Previous pregnancies	
Spontaneous	61 (8.9)
Following ICSI	60 (8.7)
Previous ectopic pregnancy	35 (5.1)
Previous abortion	
Before week 12	31 (4.5)
After week 12	6 (0.9)
Polycistic ovarian syndrome	16 (2.3)
Number of transferred grade A embryos	
0	36 (5.2)
1	95 (13.8)
≥2	556 (80.9)
Number of transferred grade B embryos	
0	510 (74.2)
1	128 (18.6)
2 or 3	49 (7.2)
Number of transferred grade C embryos	
0	671 (97.7)
1	12 (1.7)
2 or 3	2 (0.2)

Data are reported as number of patients (%) or mean (± standard deviations).

ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization

Table 2. Inherited and acquired thrombophilia in study population

Type of thrombophilia	Patients		
	Positive	Tested	%
Inherited thrombophilia			
Protein S deficiency	15	629	2.4
Protein C deficiency	8	624	1.3
Antithrombin deficiency	4	502	0.8
Hyperhomocysteneimia	32	626	5.1
Factor II mutation (G20210A)	21	626	3.4
Heterozygous	21		
Homozygous	0		
Factor V mutation	34	624	5.5
Heterozygous	33		5.3
Homozygous	1		0.2
Acquired thrombophilia			
Lupus anticoagulant	20	597	3.4
Anti-cardiolipin antibodies	31	622	5.0
IgM	15		2.4
IgG	12		1.9
IgM and IgG	4		0.7
Sapporo criteria			
IgM	2		0.3
IgG	0		0
Anti-beta2 glycoprotein antibodies	12	467	2.6
IgM	4		0.8
IgG	4		0.8
IgM and IgG	4		0.8
Sapporo criteria			
IgM	3		0.6
IgG	0		0
Lupus anticoagulant, anti-cardiolipin or anti-beta2 glycoprotein antibodies	57	655	8.7
Single positive	51		7.8
Double positive	6		0.9
Triple positive	0		0

Table 3. Association between live birth and multiple or individual thrombophilia

Thrombophilia	Live birth		OR (95% CI)
	No	Yes	
Multiple thrombophilia (≥2)	19/546	3/138	0.62 (0.18 to 2.11)
Any thrombophilia (≥1)	126/546	23/138	0.67 (0.41 to 1.09)
Protein S deficiency	11/506	4/121	1.54 (0.48 to 4.92)
Protein C deficiency	7/499	1/121	0.59 (0.07 to 4.81)
Hyperhomocysteneimia	28/498	4/126	0.55 (0.19 to 1.60)
Prothrombin mutation	19/502	2/122	0.42 (0.10 to 1.84)
Factor V Leiden	27/504	6/118	0.92 (0.38 to 2.21)
Antithrombin deficiency	4/394	0/105	NA
Positivity to Lupus anticoagulant	16/477	4/118	1.01 (0.33 to 3.08)
Positivity to Anti-cardiolipin antibodies	28/499	3/120	0.43 (0.13 to 1.44)
Positivity to Anti-beta2 glycoprotein antibodies	12/362	0/104	NA
Positivity to lupus anticoagulant, Anti-cardiolipin antibodies or beta2 glycoprotein antibodies	50/524	7/128	0.54 (0.25 to 1.15)

CI = confidence intervals; ; OR = odds ratio

Highlights

- The presence of two or more thrombophilic defects was infrequent in women undergoing in-vitro fertilization
- The effects of multiple thrombophilic defects on outcomes of in-vitro fertilization remain unclear.
- Live birth was lower with one or more thrombophilia, albeit differences were not significant.

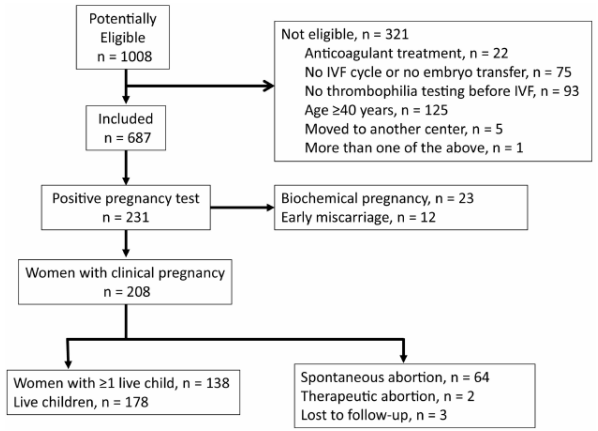
Potentially Eligible n = 1008
Not eligible, n = 321
Anticoagulant treatment, n = 22
No IVF cycle or no embryo transfer, n = 75
No thrombophilia testing before IVF, n = 93
Age ≥40 years, n = 125
Moved to another center, n = 5
More than one of the above, n = 1
Included n = 687
Positive pregnancy test n = 231
Biochemical pregnancy, n = 23
Early miscarriage, n = 12
Women with clinical pregnancy n = 208
Women with ≥1 live child, n = 138
Live children, n = 178
Spontaneous abortion, n = 64
Therapeutic abortion, n = 2
Lost to follow-up, n = 3

Figure 1